As one example of the use of the term "synthetic oligonucleotide" in the art, The McGraw-Hill Encyclopedia of Science & Technology (McGraw-Hill, 1997, volume 12, page 358) states in an article about oligonucleotides:

> ... deoxyribooligonucleotides and ribooligonucleotides of defined sequence can be obtained by using restriction endonucleases and ribonucleases, respectively. ...Chemical synthesis of oligonucleotides is, however, the preferred procedure for preparing a deoxyribooligonucleotide or ribooligonucleotide of defined sequence. The sequence is usually completed on silica gel or glass, where the first nucleotide is joined covalently to these inorganic matrices. Additional nucleotides are chemically added sequentially to the first in order to form the oligonucleotide of defined sequence. The synthetic oligonucleotide is removed from the support, purified, and used for various biochemical experiments. (emphasis added)

This reference clearly distinguishes between oligonucleotides formed enzymatically and those formed by chemical synthesis, and refers to the latter as "synthetic oligonucleotides."

As another example of the use of the term "synthetic oligonucleotide" in the art, the textbook Molecular Biology of the Cell, Third Edition (Garland Publishing, 1994, page 305) states:

> [a]t the same time that microbiologists were developing DNA cloning techniques, organic chemists were improving the methods for synthesizing short DNA chains. Today, such synthetic DNA oligonucleotides are routinely produced by machines that can automatically synthesize any DNA sequence up to 120 nucleotides long overnight. (emphasis added)

Hence, the latter reference also identifies "synthetic oligonucleotides" as oligonucleotides prepared by chemical synthesis. Copies of the relevant portions of these two references are included with this response as Attachment A and Attachment B.

In contrast, in a section of the Office Action entitled "Response to Arguments" (page 4) the Examiner constructed a definition of "synthetic oligonucleotide" from a definition of "synthetic" found in the Academic Press Dictionary of Science and Technology. The definition cited by the Examiner defines synthetic to mean "any product or item that is the result of human technology rather than something that exists in nature." Based on this definition, the Examiner concluded that

> [t]he labeled cDNA and the labeled genomic DNA of Lashkari are products that result from human technology and do not exist in nature.... Therefore, the labeled cDNA and the labeled genomic DNA are encompassed by the claimed "synthetic oligonucleotides."

LAW OFFICES OF
SKJERVEN MORRILL
MACPHERSON LLP

25 METRO DRIVE
SUITE 700
SAN JOSE, CA 95110
(408) 453-9200
FAX (408) 453-7979

Applicant respectfully submits that the Examiner has misconstrued the term "synthetic oligonucleotide." As demonstrated above, "synthetic oligonucleotide" has a clear meaning to one of ordinary skill in the art. Hence, it is unnecessary and inappropriate to construct a definition for "synthetic oligonucleotide" by juxtaposing a definition of "synthetic" with an (implicit) definition of "oligonucleotide" as the Examiner has done.

Moreover, even the dictionary cited by the Examiner supports Applicant's construction of "synthetic oligonucleotide." The dictionary cited by the Examiner provides three definitions of "synthetic." The Examiner selected the definition indicated by the dictionary to be appropriate for engineering. The same dictionary provides an alternate definition of "synthetic" that it indicates is appropriate for chemistry: "relating to compounds formed artificially by chemical synthesis." Since oligonucleotides are chemical compounds, the latter definition is the appropriate definition. Using the latter definition, "synthetic oligonucleotides" as recited in Claim 1 are oligonucleotides "formed artificially by chemical synthesis."

The Examiner asserts in paragraph 3 of the Office Action that Lashkari et al. discloses "hybridizing the microarray with a mixture of labeled synthetic oligonucleotides" at page 13058, left column, second paragraph. The cited and adjacent portions of Lashkari et al. disclose hybridizing an array with cDNA or with genomic DNA. One of ordinary skill in the art would recognize that cDNA and genomic DNA are prepared by enzymatic methods, rather than by chemical synthesis. For example, the paragraph of Lashkari et al. cited by the Examiner describes preparation of genomic DNA using Klenow enzyme. Hence, as demonstrated above, one of ordinary skill in the art would not regard cDNA and genomic DNA as "synthetic oligonucleotides."

The "synthetic oligonucleotides" recited in Claim 1 are also distinguishable from cDNA and genomic DNA by molecular size. One of ordinary skill in the art would recognize that the term "oligonucleotide" typically refers to a polymer containing less than about 100 nucleotides. For example, the encyclopedia article included as Attachment A and cited above states on page 357 that "[f]ragments containing up to 50 nucleotides are generally termed oligonucleotides...." In contrast, one of ordinary skill in the art would recognize that cDNA and genomic DNA materials typically contain 100 to 5000 nucleotides. Hence, such cDNA and genomic DNA materials are not properly described as oligonucleotides, much less as "synthetic oligonucleotides."

LAW OFFICES OF
SKJERVEN MORRILL
MACPHERSON LLP

25 METRO DRIVE
SUITE 700
SAN JOSE, CA 95110
(408) 453-9200
FAX (408) 453-7979

For the above reasons, Claim 1 is patentable over Lashkari et al. Claims 8, 9, 12, 14, 17, 18, 21 and 24, directly or indirectly dependent on Claim 1, are patentable over Lashkari et al. for at least the reasons for which Claim 1 is patentable over Lashkari et al.

Claims 1, 5, 8, 11, 12, 14, 17, 18, 21, 24, and 26 are rejected under 35 U.S.C. §102(b) as anticipated by or, in the alternative, under 35 U.S.C. §103(a) as obvious over Brown et al. (U.S. Patent No. 5,807,522). Applicant respectfully traverses this rejection.

The Examiner states in paragraph 5 of the Office Action that Brown et al. discloses

> ...hybridizing the microarray with a mixture of labeled synthetic oligonucleotide i.e. cloned DNA fragments wherein the mixture comprises oligonucleotides complementary to the genomic segments....

The passage in Brown cited by the Examiner to support his statement reads in part:

> [a] mixture of the labeled cDNAs from the two cell types is added to an array of polynucleotides representing a plurality of known genes derived from the two cell types, under conditions that result in hybridization of the cDNAs to complementary-sequence polynucleotides in the array. (column 4, line 60 to column 5, line 8, emphasis added)

As demonstrated above, cDNAs as disclosed by Brown et al. are distinguishable from the "synthetic oligonucleotides" recited in Claim 1. Hence the disclosure of Brown et al. does not anticipate Claim 1.

The obviousness rejection of Claim 1 over Brown et al. was directed to the portion of Claim 1 which recites "amplifying a plurality of genomic segments" rather than to the portion which recites "hybridizing the microarray with a mixture of labeled synthetic oligonucleotides...." Since Brown et al. does not teach or suggest "hybridizing the microarray with a mixture of labeled synthetic oligonucleotides," the Examiner has not met the requirements of a *prima facie* case of obviousness as set forth, for example, in the MPEP §2142.

For the above reasons, Claim 1 is patentable over Brown et al. Claims 5, 8, 11, 12, 14, 17, 18, 21, and 24, directly or indirectly dependent on Claim 1, are patentable over Brown et al. for at least the reasons for which Claim 1 is patentable over Brown et al.

Independent Claim 26 also recites "hybridizing the microarray with a mixture of labeled synthetic oligonucleotides...." Hence Claim 26 is patentable over Brown et al. for at least the reasons for which Claim 1 is patentable over Brown et al.

Claims 3, 4, 6, 7, 9, and 10 are rejected under 35 U.S.C. §103(a) as obvious over Brown et al. This rejection is respectfully traversed. Claims 3, 4, 6, 7, 9, and 10, directly or

LAW OFFICES OF
SKJERVEN MORRILL
MACPHERSON LLP

25 METRO DRIVE
SUITE 700
SAN JOSE, CA 95110
(408) 453-9200
FAX (408) 453-7979

indirectly dependent on Claim 1, are patentable over Brown et al. for at least the reasons for which Claim 1 is patentable over Brown et al.

Claims 13, 15, 16, and 25 are rejected under 35 U.S.C. §103(a) as obvious over Brown et al. in view of Wang et al. This rejection is also respectfully traversed. Wang et al. does not remedy the defects of Brown et al. with respect to Claim 1. Consequently, Claim 1 is patentable over Brown et al. in view of Wang et al. Claims 13, 15, 16, and 25, directly or indirectly dependent on Claim 1, are patentable over Brown et al. in view of Wang et al. for at least the reasons for which Claim 1 is patentable over this combination.

Claims 19-20 and 22-23 are rejected under 35 U.S.C. §103(a) as obvious over Brown et al in view of Fodor et al. This rejection is respectfully traversed. Fodor et al. does not remedy the defects of Brown et al. with respect to Claim 1. Hence, Claim 1 is patentable over Brown et al. in view of Fodor et al. Claims 19-20 and 22-23, directly or indirectly dependent on Claim 1, are patentable over Brown et al. in view of Fodor et al. for at least the reasons for which Claim 1 is patentable over this combination.

For the above reasons, Applicant respectfully requests reconsideration and allowance of Claims 1 and 3-26. Should the Examiner have any questions concerning this response, the Examiner is invited to call the undersigned at (408) 453-9200.

EXPRESS MAIL LABEL NO:
EL 701021669 US

Respectfully submitted,

Mark E. Schmidt

Mark E. Schmidt, Ph.D.
Agent for Applicants
Reg. No. 47,063

LAW OFFICES OF
SKJERVEN MORRILL
MACPHERSON LLP

25 METRO DRIVE
SUITE 700
SAN JOSE, CA 95110
(408) 453-9200
FAX (408) 453-7979